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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,443	LINDER ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-23 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on July 25, 2006 is acknowledged and has been entered. Claims 1 and 28 have been amended. Claims 24-25 and 30-35 have been canceled. Claims 1-23 and 26-29 are pending.

Claims 1-23 and 26-29 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL as necessitated by Applicant's amendments to the claims.

PREVIOUS REJECTIONS

The objection to claims 24-25 as being improper dependent is withdrawn in view of Applicant's cancellation of the claims. The rejection of claims 1-4, 8-9, 11-12, 14-16, 18-25, 27-28 under 35 U.S.C. 102(e) as being anticipated by Bresser is withdrawn in view of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 102

1. Claim 28 is rejected under 35 U.S.C. 102(e) as being anticipated by Lorincz et al. (US Patent 6,969,585; November 2005). Lorincz teaches a universal collection medium for cell

collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

With regard to claim 28, Lorincz teach a method for identifying a sensor which specifically binds to a desired target, comprising:

a) contacting a sample suspected of containing a target of interest with a detectable sensor, wherein said contacting takes place in a preservative solution comprising an amount of one or more water soluble alcohols effective to preserve such solution against at least one contaminant (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection; col. 10, where the formulation of the universal collection medium are listed, which comprise an alcoholic preservative solution; see Examples 3-5, where samples were incubated and hybridized in UCM formulations indicated at col. 10); and

b) detecting whether said sensor has bound to said target (Example 1, col. 10, lines 1-5, where the plate was read in a luminometer and data was expressed as signal-to-noise).

Claim Rejections - 35 USC § 103

2. Claims 1-4, 8-12, 14-16, 18-19 and 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz et al. (US Patent 6,969,585; November 2005) as applies to claim 28 above and further in view of Shah et al. (US Patent 6,165,723; December 2000). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

With regard to claim 1, Lorincz teach a method comprising:

a) providing a sample that is suspected of containing a target (example 1, col. 10, where the protocol of detecting a nucleic acid is taught; example 3-5, the samples were HPV 16 positive cancer cells, CaSki were placed in the universal collection medium and tested for HPV DNA or RNA targets);

b) providing a sensor that can bind to the target in an alcoholic preservative solution, said sensor conjugated to a chromophore (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection; col. 10, where the formulation of the universal collection medium are listed, which comprise an alcoholic preservative solution; see Examples 3-5, where samples were incubated and hybridized in UCM formulations indicated at col. 10);

c) contacting the sample with the sensor in the alcoholic preservative solution under conditions in which the sensor can bind to the target, if present (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection); and

e) detecting the target (Example 1, col. 10, lines 1-5, where the plate was read in a luminometer and data was expressed as signal-to-noise).

With regard to claim 2, Lorincz teach an embodiment of claim 1, wherein the sample is selected from the group consisting of a urine, a vaginal swab, a pap smear, a needle biopsy and a

section of tissue (col. 7, lines 46-57, where multiple methods of obtaining cells are noted, including those listed).

With regard to claims 3 and 4, Lorincz teach an embodiment of claim 1, wherein the sensor comprises an aptamer and a polynucleotide (col. 2, lines 59-61, where DNA, RNA, protein or carbohydrates are measured; col. 9, lines 32-39).

With regard to claim 14, Lorincz teach an embodiment of claim 1, wherein the target is DNA (col. 2, lines 59-61, where DNA, RNA, protein or carbohydrates are measured; col. 9, lines 32-39).

With regard to claim 15, Lorincz teach an embodiment of claim 1, wherein the target is RNA (col. 2, lines 59-61, where DNA, RNA, protein or carbohydrates are measured; col. 9, lines 32-39).

With regard to claim 16, Lorincz teach an embodiment of claim 1, wherein the sample is a cellular fraction (Example 3-5, where HPV 16 positive cancer cells (CaSki) were placed in UCM and other fixatives and where the cells were studied at a concentration of $0.8x\ 10^6$ cells).

With regard to claim 18, Lorincz teach an embodiment of claim 1, wherein said target is a pathological organism or component or product thereof (Examples 3-5, where the target is HPV).

With regard to claim 19, Lorincz teach an embodiment of claim 1, wherein the target is a virus or component or product thereof (Examples 3-5, where the target is HPV).

With regard to claim 23, Lorincz teach an embodiment of claim 1, further comprising washing said sample prior to said detecting (Example 1, col. 10, lines 64-66, where wells were washed 6x after hybridization and prior to detection).

With regard to claim 24 and 25, Lorincz teach an embodiment of claim 1, wherein the sensor is conjugated to a detectable moiety and where the sensor is itself detectable (Example 1, where the DNA/RNA protocol was taught, where a DNA biotinylated probe was added directly to samples and incubated at 65°C for hybridization, followed by transfer to a streptavidin coated microplate, followed by chemiluminescent detection).

With regard to claim 26, Lorincz teach an embodiment of claim 1, wherein the method is automated (col. 9, lines 46-67, where the method can be carried out using devices adapted to the method).

With regard to claim 27, Lorincz teach an embodiment of claim 1, wherein the method is performed manually (col. 9, lines 46-67, where in the converse situation, the method can be carried out without using devices adapted to the method).

Regarding claim 1, Lorincz teaches the method of binding a sensor to a target in an alcohol containing solution, however Lorincz does not teach the steps directed to d) applying a light source to the solution that can excite the chromophore and e) detecting whether light is emitted from the target.

With regard to claim 8, Shah teach an embodiment of claim 1, wherein the chromophore is a fluorophore (col. 9, lines 5-30, where a fluorescein labeled probe complementary to B. microti was hybridized to fixed cells).

With regard to claims 9 and 11, Shah teach an embodiment of claims 8 and 9, wherein the fluorophore is a fluorescent dye (col. 9, lines 5-30, where a fluorescein labeled probe complementary to B. microti was hybridized to fixed cells).

With regard to claim 12, Shah teach an embodiment of claim 11, wherein the fluorescent dye is fluorescein (col. 9, lines 5-30, where a fluorescein labeled probe complementary to B. microti was hybridized to fixed cells).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the probe taught by Lorincz to substitute a direct chromophore label as taught by Shah for the biotin label currently disclosed. As noted by Shah, "The sample is then rinsed with Evans Blue to counter stain the host cell, so as to see clearly fluorescent labeled probe(s) bound to specific nucleic acids of the pathogens which may be present within the sample (e.g., within the cells of the sample)" (col. 2, lines 59-63). Furthermore, as noted by Shah, "This procedure allows for the use of non-radiolabeled probes, which have a much longer shelf life and do not require special storage space. Either direct detection system using dark field microscopy can be used" (col. 6, lines 1-4). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the direct fluorescent label taught by Shah for the biotin label taught by Lorincz with a reasonable expectation for success.

3. Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Challberg et al. (WO93/10263; May 1993). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above.

However, Lorincz does not explicitly teach the inclusion of control samples in the practice of the method exemplified at Examples 1-3. Challberg teaches a technique for the detection of genetic defects, microbial infections or viral infections (Abstract).

With regard to claim 20, Challberg teach an embodiment of claim 1, further comprising comparing a result from said detecting to a result obtained from a control sample (Example 4, where samples were tested by pipetting hydrolysis reagent into control and sample tubes; Table IV).

With regard to claim 21, Challberg teach an embodiment of claim 20, where the control sample is a positive control (p. 26, lines 8-13, where a kit for practice of the disclosed method should contain a positive control, preferably 150 pm biotinylated PCR product).

With regard to claim 22, Challberg teach an embodiment of claim 20, where the control sample is a negative control (p. 26, lines 8-13, where a kit for practice of the disclosed method should contain a negative control, preferably a mock PCR reaction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Lorincz to incorporate the sample controls taught by Challberg to arrive at the claimed invention with a reasonable expectation for success. As taught by Challberg, "The kit should contain a negative control and a positive control for each probe. Preferably, the negative control is mock PCR reaction buffer. The positive control preferably contains 150 pM 5'-biotinylated PCR product in a mock PCR reaction" (p. 26, lines 8-13). Furthermore, the inclusion of both a positive and a negative control for each individual

probe in the assay ensures reproducibility and reliability of each replicate of the assay. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the control samples taught by Challberg to the method of target detection taught by Lorincz to achieve reliable and sensitive detection of target sequences, and HPV infection, specifically.

4. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) as applied to claim 28 above, and further in view of Challberg et al. (WO93/10263; May 1993). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz teaches all of the limitations of claim 29 as recited in the 102 rejection stated above. However, Lorincz doesn't teach the application of the method of claim 1 to a plurality of candidate sensors. Challberg teaches a technique for the detection of genetic defects, microbial infections or viral infections (Abstract).

With regard to claim 29, Challberg teaches an embodiment of claim 28, wherein the method is performed on a plurality of candidate sensors (p. 26, Example 1, where Probes A, B and C were incorporated into the method of detection and wherein each of these probes were specific for a plurality of types of HPV virus).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Lorincz to incorporate the plurality of candidate sensors taught by Challberg to arrive at the claimed invention with a reasonable

expectation for success. As taught by Challberg, "Numerous types of HPV have been identified, and not all HPV infections are oncogenic. For example, HPV 6 and HPV 11 are associated with benign lesions, whereas HPV 16 and HPV 18 are detected in cervical and other anogenital cancers and their precursor lesions. The determination of the type of HPV infection is therefore essential for proper diagnosis, risk assessment of cancer development and treatment". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the plurality of candidate sensors taught by Challberg into the method of detection taught by Lorincz to achieve proper determination of the specific viral types present in the sample(s) being tested.

5. Claim 5, 7, 29 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Hyldig-Nielsen et al. (US Patent 6,280,946; August 2001). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion of a probe which comprises peptide nucleic acid (PNA) or the inclusion of a plurality of probes each of which comprises a corresponding detectable label.

Hyldig-Nielsen teaches the inclusion of a peptide nucleic acid probe into a method of multiplex-FISH analysis (Abstract).

With regard to claim 5, Hyldig-Nielsen teach an embodiment of claim 1, wherein the sensor comprises a peptide nucleic acid (Abstract, col. 10, lines 58-66, where PNA probes represent a preferred embodiment of the invention).

With regard to claim 7, Hyldig-Nielsen teach an embodiment of claim 1, wherein the sample is contacted with a plurality of different sensors, each of said plurality comprising a corresponding detectable label, wherein each of said plurality can selectively bind to a corresponding different target (col. 7, lines 58-63, where the invention is directed towards multiplex analysis; col. 15, lines 60-63, where each individual probe is independently detectable).

With regard to claim 29, Hyldig-Nielsen teach an embodiment of claim 28, wherein the method is performed on a plurality of candidate sensors (col. 7, lines 58-63, where the invention is directed towards multiplex analysis; col. 15, lines 60-63, where each individual probe is independently detectable).

With regard to claim 36, Hyldig-Nielsen teach an embodiment of claim 1, wherein said target is a bacterium or component or product thereof (Table 2, where PNA probes are directed to detect bacteria; Example 12, col. 28, lines 26-43, where a culture of *E. coli* is examined using the multiplex-PNA-FISH method disclosed).

With regard to claim 37, Hyldig-Nielsen teach an embodiment of claim 1, wherein said target is a yeast or component or product thereof (Table 2, where PNA probes are directed to detect eucarya; Example 12, col. 28, lines 44-65, where a culture of *Saccharomyces cerevisiae* is examined using the multiplex-PNA-FISH method disclosed).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the PNA probe and the plurality of probes taught by Hyldig-Nielsen into the method of hybridization and detection of nucleic acids. As noted by Hyldig-Nielsen, the inclusion of PNA probes specifically provides that "Because the PNA probe can efficiently and preferably, hybridize to nucleic acid under these conditions of low salt, the PNA probes can be designed to target rRNA which cannot be targeted by traditional nucleic acid probes". Hyldig-Nielsen goes on to note that "PNA probes of this invention typically generate stronger signals than can be achieved with nucleic acid probes of comparable nucleobase sequence" (col. 14, lines 30-45). Furthermore, Hyldig-Nielsen teaches that, "the ability to differentiate between and/or quantitate each of the independently detectable moieties provides the means to multiplex a hybridization assay because the data which correlates with the hybridization of each of the distinctly (independently) labeled probe to a particular target sequence can be correlated with the presence, absence or quantity of each organism sought to be detected in the sample. Consequently, the multiplex assays of this invention may be used to simultaneously detect the presence, absence or quantity of two or more organisms in the same sample and in the same assay" (col. 7, line 66 to col. 8 line 9). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the PNA probes as described by Hyldig-Nielsen into the method of nucleic acid detection taught by Lorincz in order to achieve the stated benefit of increased signal strength and probes which target regions inaccessible to traditional nucleic acid probes with a reasonable expectation for success.

6. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Kumar et al. (Bioorganic & Medicinal Chemistry, 1998, vol. 8, p. 2219-2222). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion of a probe which comprises locked nucleic acid.

Kumar teaches the improvement of duplex stability provided by the inclusion of a locked nucleic acid probe into a method where recognition of complementary DNA or RNA was necessary (Abstract).

With regard to claim 6, Kumar teach an embodiment of claim 1, wherein the sensor comprises a locked nucleic acid (Abstract, p. 2219, where it is noted that LNA provides stability against 3'-exonucleolytic degradation, efficient automated synthesis, good solubility and improved stability of duplexes with DNA or RNA).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the LNA probe taught by Kumar into the method of nucleic acid detection taught by Lorincz. As noted by Kumar, the inclusion of LNA probes specifically provides, "unprecedented thermal stabilities of duplexes towards complementary DNA and RNA" , stability towards 3'-exonucleolytic degradation, efficient automated oligomerization and good aqueous solubility (p. 2219). Therefore, one of ordinary skill in the art at the time the

invention was made would have been motivated to include the LNA probe taught by Kumar in order to achieve the stated benefit of improved thermal stability of duplexes formed with either DNA or RNA target molecules.

7. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Bruchez, Jr. et al. (Science, 1998, vol. 281, p. 2013-2016). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion of a semiconductor nanocrystal as the detectable label.

Bruchez, Jr. teaches the inclusion of a semiconductor nanocrystal into a method of biological staining and diagnostics (Abstract).

With regard to claim 10, Bruchez, Jr. teach an embodiment of claim 9, wherein the fluorophore is a semiconductor nanocrystal (Abstract, Figure 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the semiconductor nanocrystal taught by Bruchez, Jr. into the method of nucleic acid detection taught by Lorincz. As noted by Bruchez, Jr, the semiconductor nanocrystal label provide the benefit that "many sizes of nanocrystals may therefore be excited with a single wavelength of light, resulting in many emission colors that may be detected

simultaneously" (p. 2014, col. 1). Furthermore, Bruchez, Jr. teach that "the tenability of the optical features allows for their use as direct probes or as sensitizers for traditional probes. These nanocrystals also have a long fluorescence lifetime, which can allow for time-gated detection of autofluorescence suppression" (p. 2015, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the semiconductor nanocrystal taught by Bruchez, Jr. in order to achieve the stated benefit of a label that is excitable by a single wavelength of light yet able to provide multiple colors of emission, particularly for the detection of multiple targets simultaneously.

8. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Ylikoski et al. (US Patent 5,256,535; October 1993). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above. However, Lorincz does not teach the inclusion of a lanthanide chelate as the detectable label.

Ylikoski teaches the inclusion of a lanthanide chelate into a method of hybridization (Abstract).

With regard to claim 13, Ylikoski teach an embodiment of claim 9, wherein the fluorophore is a lanthanide chelate (Abstract; col. 3, lines 44-52; col. 4, lines 17-21).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the lanthanide chelate label taught by Ylikoski into the method of nucleic acid detection taught by Lorincz. As noted by Ylikoski, the inclusion of a lanthanide chelate label specifically provide that "the intensity of fluorescence emitted from the double stranded nucleic acid is a quantitative measure of the nucleotide sequence to be determined" (col. 4, lines 25-28). Ylikoski goes on to note that "the important feature in the invention is the use of water soluble polymeric compounds as a matrix to which a large number of europium or terbium chelates are covalently coupled. This covalent coupling gives a large amplification of the detectable signal" (col. 4, lines 35-42). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the lanthanide chelate label taught by Ylikoski in order to achieve the stated benefit of increased signal strength with a reasonable expectation for success.

9. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lorincz (US Patent 6,969,585; November 2005) in view of Shah et al. (US Patent 6,165,723; December 2000) as applied to claims 1-4, 8-12, 14-16, 18-19 and 23-27 above, and further in view of Fukasawa et al. (Science, 1996, vol. 271, p. 1744-1747). Lorincz teaches a universal collection medium for cell collection which allows for cytology and direct molecular analysis on cells preserved in a single sample (Abstract).

Lorincz in view of Stahl teach all of the limitations of claims 1-4, 8-12, 14-16, 18-19 and 23-27 as recited in the 103 rejection stated above.. However, Lorincz does not teach the examination of a centrosomal target.

Fukusawa teach an examination of centrosomes in cells where the p53 tumor suppressor gene is mutated (Abstract).

With regard to claim 17, Fukusawa teach an embodiment of claim 1, wherein the target is centrosomal (Abstract, Figures 1-2, where centrosomes were identified in mouse embryonic fibroblasts with wildtype and mutated p53 using an antibody to γ-tubulin).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the centrosomal target taught by Fukusawa into the method of nucleic acid detection taught by Lorincz. As noted by Fukusawa, the centrosomal target was crucial and in cells where p53 was mutated, "the presence of multiple centrosomes in the mitotic spindles had profound effects on chromosome segregation; the chromosomes did not partition during anaphase because they were captured by astral microtubules of one centrosome (or a few centrosomes) localized outside of the poles". Fukusawa goes on to note that "when large numbers of centrosomes failed to localize at the poles in a bipolar fashion, the proper spindle apparatus did not form" (p. 1746, col. 1-2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to include the centrosomal target taught by Fukusawa in order to determine the proper chromosomal segregation in a cellular target with a reasonable expectation for success.

Response to Arguments

10. Applicant's arguments filed July 25, 2006 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claim 28 under 35 U.S.C. 102 as being anticipated by Lorincz and also the rejection of claims 1-4, 14-16, 18-19 and 23-27 under 35 U.S.C. 103(a) as being unpatentable over Lorincz in view of Shah.

Regarding Lorincz, Applicant disagrees with Examiner's previous rejection and state that "Example 1 of Lorincz states that the assay for nucleic acids follows '...in general principle the method for detecting HIV RNA by the Digene Hybrid Capture HIV Test described in WO93/10263' (see column 10, last paragraph). The method taught in WO93/10263 is exemplified in Example 1 of the application. In Example 1, the method clearly requires that '...after hydrolysis, a 150 ul aliquot was removed from the sample tube and added to 50 ul of a probe diluent containing Probe A, B or C (see page 26, line 29-31). Thus the contacting of a target of interest with a detectable sensor does not take place in Lorincz in a preservative solution as specified by the current claims." (p. 6 of remarks).

Examiner respectfully disagrees with Applicant's reading and interpretation of the method of analysis taught by Lorincz, which anticipates or renders obvious the rejected claims of the instant application. The portion of the WO93/10263 highlighted by Applicant does indicate that an aliquot of the sample was removed from the original tube/container and added to a probe diluent. However, there appears to be no indication that the original preservative solution in which the sample was maintained (ViraPap™ in this instance) was no longer present in the sample following the hydrolysis step. Therefore, presuming that the method taught by Lorincz actually follows the specific method steps disclosed in the WO93/10263 document, the contacting does take place in a composition comprising the preservative solution.

However, it is noted that the disclosure of Lorincz, following the portion cited by Applicant, goes on to note "Briefly, following lysis, 50 ul of probe mix (containing DNA biotinylated probe) was added to each well. The plate was sealed and incubated at 65oC for 1.5 hours for hybridization to occur" (col. 10, lines 58-61). This statement indicates that the contacting does, indeed, occur in the presence of the preservative solution disclosed by Lorincz. While it is not explicitly stated that "each well" contains preservative, the entire disclosure of Lorincz is directed to preserving samples and also to allow for "direct molecular analysis on cells preserved in a single sample" (Abstract). The general method of nucleic acid analysis exemplified in Example 1 is directed to the detection and enumeration of mRNA copies per cell. It is noted that, regarding the analysis of RNA, Lorincz teaches "In one embodiment of the present invention RNA was analyzed directly by solution based procedures. The cells were first lysed by adding a proteolytic enzyme to the cells contained in the wells of a microtiter plate" (col. 9, lines 11-14) (emphasis added). Furthermore, regarding the practice of detection of RNA, "After incubation, biotinylated DNA probes were added to each well. The RNA:DNA hybrids were captured onto a solid phase by transferring to streptavidin coated microplates. Alkaline phosphatase-conjugated antibodies to RNA:DNA hybrids were added to each well in the hybridization microplate and signals were generated by adding a chemiluminescent reagent such as CDP-Star™ with Emerald II (Tropix) to each well. The signal was read from the microplate" (col. 9, lines 16-23). These teachings are in line with the general method disclosed in Example 1, as well and indicate that the hybridization does occur in solution.

Finally, it is also noted that Lorincz states "Cell samples for use in the method of the present invention can be fixed or processed in any manner consistent with the assays to be

performed. For example, both cytological and molecular assays can be performed using cells fixed on a solid substrate such as a slide. Preferably, however, molecular assays are done in solution" (col. 8, lines 10-18). Therefore, considering these teachings by Lorincz, in addition to the methods of detection in the preservative solution disclosed in Examples 2 and 3, where HC II RNA or DNA were assayed in the presence of UCM formulations 127, 128, 130 and the Digene control using the Hybrid Capture II HPV DNA or RNA tests, Examiner respectfully disagrees with Applicant's arguments regarding the Lorincz reference.

Relevant prior art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Lader (US Patent 6,204,375; March 2001) discloses a reagent for preserving and protecting the RNA content of tissue samples prior to RNA isolation. Ryan (US Patent 6,337,189; January 2002) teaches a system and composition for the stabilization of biological specimens which employs a fixative that comprises an organic solvent which includes alcohol.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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